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AN EXPERIMENT WITH RABBITS

BY

ALEKSIS TÄHKA, MARTTI TURUNEN and LARS HJELT

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MERCATORIN KIRJAPAINO
HELSINKI, FINLAND

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INTRODUCTION AND PROBLEMS

Surgical treatment of the heart has brought numerous problems of various kinds. In comparison to the surgical treatment of other organs, heart surgery possesses several special features. Also postoperatively the organ must function without interruption, for the blood must continuously obtain its impulsion and correct direction of flow. In association with the operation there may arise coagula which may enter the circulating blood stream, or earlier formed coagula may begin to circulate. Furthermore, the special structure of the myocardium is different from that of other muscular tissues. The continuous action of the heart muscle may interfere with its healing. Tissue already cicatrised also may stretch and even tear, resulting in aneurysms or ruptures.

Our knowledge of the behaviour of heart muscle towards trauma is chiefly based on observations of the healing of myocardial traumas and infarctions and of contusions of the heart. The purpose of the present experiments was to study the healing of experimentally made and sutured incision wounds penetrating the heart, since such wounds are of major interest from the surgical point.

Macroscopically we paid attention to adhesions which had developed in the pericardium and to macroscopic changes in the heart muscle, such as for example distended areas in any region of the heart or in the vicinity of the scar. The presence of blood coagula within the heart was also examined. Microscopically we studied changes in the region of the wound and in its immediate vicinity, with special attention to the time of their development.

REVIEW OF THE LITERATURE

The healing of lesions in tissues of different types has been a subject of active study. The primary healing of a well sutured wound is concurrent with minor inflammatory changes. The end result is a small scar. The epithelium is fully regenerated and subcutaneous fat and striated muscle are replaced by cicatricial tissue. In addition to epithelium, only the endothelium of blood vessels and connective tissue is capable of regeneration (E. L. Howes 1954, M. Allgöwer 1956).

The special conditions in the heart from the point of view of healing were commented upon already in 1939 by G. K. Mallory, P. D. White and J. Salcedo-Salgar. After injury the myocardium must continue its function. Comparative rest for the heart is attained by keeping the patient in bed. Since the introduction of hibernation, the heart can be temporarily relieved by depressing the patient's metabolic processes. The attempts made to prepare an artificial heart illustrate the significance which is given in operative treatment to temporary isolation of the heart from its function.

As stated by, e. g., E. F. Bright and C. S. Beck (1935), puncture wounds and shot wounds were the first diseases of the heart to be taken into the field of surgery, since they require rapid surgical attention. Fischer, in 1868, published a paper, which still is considered valuable, on traumatic cardiac and pericardial wounds on the basis of 452 cases collected from the literature or treated by him. Among these cases, 401 involved the pericardium and myocardium, and only 51 involved the pericardium alone. The purpose of the paper was to refute the opinion then prevalent that wounds in the heart or its surrounding membranes were unavoidably fatal. Case reports have been published of the surgical treatment of traumatic heart wounds, and fresh wounds have been examined at autopsy; however, these reports have not been of much assistance in the study of the healing process of wounds of the heart. R. L. Sanders (1935) pointed out that most of the known traumas of the heart were penetrating wounds. They usually prove fatal before the patient reaches treatment.

Bright and Beck studied experimentally induced heart contusions in 25 dogs. The pericardium was opened under anesthesia and repeated aseptic blows were given locally in the region of the

right or left ventricle. Twenty dogs endured the treatment well, although there was hemorrhagic swelling of the myocardium and it seemed apparent that softening and rupture would definitely follow. The ECG became normal within 2—3 months. The animals were sacrificed 2—3 months after the operation. They were at this time in a good condition and it was surprising to observe how well the myocardial lesion had become repaired. In three samples there were no signs of a myocardial trauma, and no adhesions were demonstrable. In 14 samples there were adhesions between the parietal pericardium and the epicardium. In 9 of these cases the adhesions were limited to the contused area of the myocardium. In no sample was the entire heart muscle penetrated by cicatricial tissue. Signs of development of a myocardial aneurysm were not seen in a single case, but the animals were, as said, killed already 3 months after treatment.

One of the dogs in the experiments of Bright and Beck died of rupture of the myocardium during the treatment, and two died of ventricular fibrillation; in these cases there was hemorrhage in the interventricular septum. Two dogs died of cardiac insufficiency. Both dogs had a very rapid pulse rate, and one died within a few hours and the other on the following day.

C. S. Beck (1935) collected 175 cases of trauma of the heart. In his opinion the number of contusions of the heart is much greater than generally has been diagnosed, since the heart is capable of enduring a great deal of violence. On the basis of the series published by him, Beck concluded that softening of the myocardium is at its maximum during the second week.

Traumas of the pericardium were dealt with by S. F. Crynes and W. C. Hunter (1939) in the light of cases collected in the literature and of their own autopsy material. Rupture of the pericardium is merely one of many simultaneous traumas, and in most cases it has only slight or no effect on the cause of death. Among 4107 consecutive autopsies they encountered 22 pericardial ruptures. In one case death took place 2½ years after occurrence of the trauma, the heart protruding through the ruptured pericardium. E. Warburg (1940) found that death occurring suddenly and unexpectedly a great length of time after a trauma of the heart may be of traumatic origin.

Traumatic lesions of the heart either cause immediate death

or heal, and thus they do not come on the autopsy table. On the other hand, in the study of regenerative processes occurring in the heart, myocardial infarctions have provided abundant material for study of the various stages of healing of infarcts (Cf. Gould 1953).

The rate of healing of an infarct depends upon its size. Small infarctions heal completely within five weeks, and larger ones in about two months (W. A. D. Anderson 1953). Despite the diminished blood supply, the healing of myocardial infarcts begins immediately. The necrotic tissue is removed and replaced by vascularised connective tissue. The end result is a scar, as in other healing processes.

Various complications may occur during the healing process of an infarct. In large myocardial infarcts the endocardium is involved almost without exception, thus promoting the development of thrombosis. The size of a thrombus depends upon the size of the area of endocardial destruction (Anderson 1953). On the basis of experimental studies on dog and rabbit hearts, R. Haecker (1907) concluded that a suture extending through the endocardium may promote thrombus formation in the heart. During the process of healing, a mural thrombus has a tendency to soften. A thrombus adhering to the inner wall of a ventricle does not become organised, as do small vascular thrombi. Large thrombi remain stationary for a considerable length of time even after healing of the infarction, but they appear to undergo gradual dissolution by the action of proteolytic enzymes (Anderson). During this phase, a mural thrombus is a constant threat, since portions of it may break off and now and then cause embolism.

According to Anderson, myocardial rupture is by far the most common complication of acute infarction. On the basis of a large autopsy series, Edmonson aud Hoxie (1942) analysed infarcts and concomitant ruptures. In the presence of cicatrisation in the myocardium, the danger of rupture was only one-fourth of that in non-cicatrised hearts. The stage of healing of the infarction and the amount of intraventricular pressure appear to be decisive factors in the development of rupture of the heart.

G. K. Mallory, P. D. White and J. Salcedo-Salgar (1939) studied with the aid of autopsy specimens the healing of myocardial infarctions in 72 patients. Histological findings for each day following development of the infarction gave detailed information of the

numerous events which ultimately resulted in the development of a scar. Their report contains the most detailed description available on the events leading to scar formation in the heart muscle. We shall revert to these findings in the discussion.

Among the complications following myocardial infarction, Anderson also mentioned aneurysms of the heart. Healed infarcts are composed of fibrous tissue and form relatively thin areas in the wall, since they rarely are more than one-third or one-half as thick as the normal ventricular wall. If the cicatricial areas are large, they have a tendency to stretch because of the systolic pressure. Since cicatricial tissue is inelastic, it has no contractile power, and before long the old infarct may form a saccular distention in the ventricular wall. These aneurysms are usually situated in the area of the left ventricle towards the apex of the heart. A mural thrombus frequently occupies a part of the aneurysmal sac. Occasionally the wall of the aneurysm becomes calcified. (Cf. also C. A. Elsberg 1899 and Hirschboeck 1935).

C. A. Elsberg (1899), E. Frey and G. Kuetgens (1956) and C. G. Thomas and S. E. Ziffren (1952) also made a histological study on dogs and rabbits of the events observed in association with experimentally produced traumas of the heart. It was the prevalent opinion at that time that the voluntary striated musculature was capable of regeneration. He found no signs of regeneration in the heart muscle. There first occurred necrosis of the muscle, which was greater after the use of continuous suture than of interrupted suture. From the very first day onwards he observed cellular infiltration. With disappearance of the infiltration there remained fibrous new tissue. Adjacent to the sutures in the pericardium there were polynuclear giant cells, some of which contained fragments of degenerated muscle fibres.

PRESENT INVESTIGATION

MATERIAL AND METHODS

The present experiments were made on 100 healthy adult rabbits. In the midsternal line a sterile incision was made through the soft parts under ether narcosis. The sternum was split with an arc saw. Fixation sutures were made in the pericardium, which was then cut open between the sutures. The heart was then lifted

TABLE

COMPOSITION OF THE MATERIAL

No. of Animal	Time of Killing	General Macroscopic Finding at Autopsy	Macroscopic Changes in the Heart
4	9th day after lesion		Small amount of clear fluid in pericardium. Pericardium adherent to wound area of heart. Fibrin in endocardium. N. W.
5	8th day		Pericardium adherent to wound area of heart
6	7th day		Pericardium adherent anteriorly to wound area of heart
8	6th day	Fluid present in the wound, infection	Clear fluid in pericardium. Pericardium adherent to wound area of heart
9	6th day		Pericardium adherent to wound area of heart. Abundant fluid in pericardium
10	14th day		Pericardium adherent to anterior wall of thorax and to wound area of heart
11	5th day		Pericardium adherent to anterior wall of thorax and wound area of heart. Small amount of clear fluid in pericardium
12	5th day		Pericardium adherent to anterior wall of thorax and wound area of heart. Hemorrhagic fluid ventral to pericardium and serous fluid within pericardium
13	3rd day		Pericardium adherent to wound area of heart and anterior thoracic wall
15	4th day	Hemorrhagic fluid ventral to pericardium	Pericardium adherent to anterior thoracic wall
16	8th day	Serous fluid subcutaneously	Pericardium adherent to anterior wall of thorax and to wound area of heart. Abundant seropurulent fluid in pericardium. Infection
17	2nd day		Pericardium adherent to anterior wall of thorax and wound area of heart
19	5th day		Pericardium adherent to anterior wall of thorax and wound area of heart. Abundant clear fluid in pericardium
20	1st day	Fluid between sternum and pericardium	Pericardium adherent to anterior wall of thorax

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AND MACROSCOPICAL FINDINGS

Location of Penetrating Wound	Site of Histological Specimen
Left ventricle	Wound area in wall of left ventricle
Left ventricle	Wound area in wall of left ventricle
Left ventricle. Bruise in apex produced by pincers	Wound area in wall of left ventricle. Bruised area of apex
Left ventricle	Wound area in wall of left ventricle. Bruised area of apex
Left ventricle. Pincer bruise at apex	Wound area in wall of left ventricle.
Left ventricle. Pincer bruise at apex	Wound area in wall of left ventricle. Bruised area of apex
Left ventricle. Pincer bruise at apex	Wound area in wall of left ventricle. Bruised area of apex
Left ventricle. Pincer bruise at apex	Wound area in wall of left ventricle. Bruised area of apex
Left ventricle	Wound area in wall of left ventricle
Left ventricle	Wound area in wall of left ventricle
Right ventricle	Area to which pericardium was adherent
Right ventricle	Wound area in wall of right ventricle
Left ventricle	Wound area in wall of left ventricle
Left ventricle. Pincer bruise at apex	Wound area in heart

(Cont.)

No. of Animal	Time of Killing	General Macroscopic Finding at Autopsy	Macroscopic Changes in the Heart
21	3rd day		Pericardium adherent to anterior wall of thorax and wound area of heart
23	2nd day		Pericardium adherent to anterior wall of thorax and wound area of heart. Bloody. Hemorrhagic fluid abundantly present in pericardium
24	6th day		Pericardium adherent to anterior wall of thorax and wound area of heart
25	4th day		Pericardium adherent to anterior wall of thorax and wound area of heart
26	3rd day		Pericardium adherent to anterior wall of thorax and wound area of heart
27		Died spontaneously 35 days after operation	Pericardium adherent to anterior wall of thorax. Abundant turbid opaque fluid in pericardium. Blood coagulum in right ventricle
29	16th day		Pericardium adherent to anterior thoracic wall and wound area of heart. Coagulum in right ventricle
31	21st day		Pericardium adherent to anterior thoracic wall and wound area of heart
35	28th day		Pericardium firmly adherent to anterior thoracic wall and wound area of heart. Thick layer of fibrin on surface of epicardium around the wound
36	9th day		Pericardium adherent to anterior thoracic wall and wound area of heart. Coagulum on wound in right ventricle
37	9th day		Pericardium adherent to anterior thoracic wall and wound area of heart. Small coagulum adjacent to suture in right ventricle
38	8th day		Pericardium adherent to ventral surface of heart. Coagula in right ventricle
39		On 71st postoperative day found dead of hemorrhage after fight	Pericardium adherent to apex of heart. Thin bulging area in apex of right ventricle
40		On 69th postoperative day found dead	Pericardium adherent to anterior thoracic wall and ventral surface of heart. Copious fluid in right pulmonary pleura. Right lower lobe atelectatic
41	7th day		Pericardium adherent to anterior thoracic wall and wound area of heart

Location of Penetrating Wound	Site of Histological Specimen
Left ventricle. Pincer bruise at apex	Wound area in wall of left ventricle. Apex of heart
Left ventricle	Wound area in wall of left ventricle
Right ventricle. Left ventricle. Pincer bruise at apex	Wound area in left ventricle. Wound area in apex. Wound area in wall of right ventricle
Left ventricle. Pincer bruise at apex	Wound area in heart. Apex of heart
Left ventricle. Pincer bruise at apex	Wound area in heart. Wound area in muscle
Right ventricle	Wound area in wall of right ventricle
Left ventricle	Wound area in wall of left ventricle
Left ventricle	Wound area in wall of left ventricle
Right ventricle	Wound area in wall of right ventricle
Right ventricle	Wound area in wall of right ventricle
Left ventricle. Penetrating wound by pincers into right ventricle	Wound areas in walls of left and right ventricles
Left ventricle near intraventricular septum	Wound area in wall of left ventricle
Right ventricle	Wound area in wall of right ventricle
Right ventricle	Wound area in wall of right ventricle
Left ventricle	Wound area in wall of left ventricle

(Cont.)

No. of Animal	Time of Killing	General Macroscopic Finding at Autopsy	Macroscopic Changes in the Heart
42	7th day		Pericardium adherent to anterior thoracic wall and wound area of heart. Coagulum in left ventricle
43	6th day		Pericardium adherent to anterior thoracic wall and wound area of heart. Small amount of bloody fluid in pericardium. Numerous coagula in right ventricle
45		On 62nd postoperative day found dead	Pericardium adherent to anterior thoracic wall and apex of heart. At site of the adhesion a pea-sized aren consists only of a thin membrane. Small coagulum but no fluid in pericardium
46	368th day		Pericardium adherent to anterior thoracic wall and apical region of left ventricle
47		On 14th day found dead	Pericardium, anterior surface and apex of heart adherent to anterior thoracic wall. Pericardium adherent to epicardium. Copious dark coagula in right ventricle
48	165th day		Pericardium adherent to anterior wall of pericardium and apex and wound area of heart. Wound area thin and delicate
49	3rd day		Wound area of left ventricle adherent to posterior tissues of sternum. Small coagulum in right ventricle
50	316th day		Pericardium adherent to apex of heart
51		On 57th postoperative day found dead	Pericardium non-adherent. Upper portion of left lung atelectatic and firm
52		On 9th postoperative day found dead	Pericardium adherent to wound area of heart
53	24th hour		Pericardium empty. Coagula in both ventricles
54	21st hour		Coagula in left ventricle
55	18th hour		Small amount of coagulated blood in right ventricle
56	15th hour		No coagula in ventricles
57	5th hour		No coagula in ventricles
58	4th hour		No coagula in ventricles
59	3rd hour		No coagula in ventricles
60	2nd hour		Coagula in right ventricle
62	6th hour		No coagula in ventricles
64	12th hour		Some coagula in right ventricle
68	11th hour		Small coagula in left ventricle

Location of Penetrating Wound	Site of Histological Specimen
Left ventricle near intra-ventricular septum	Wound area in wall of left ventricle
Left ventricle	Wound area in wall of left ventricle
Right ventricle	Wound area in right ventricle
Left and right ventricles	Wound areas in walls of left and right ventricles
Right ventricle	Wound area in wall of right ventricle
Right auricle	Sutured wound in right auricle
Left and right ventricles. Pincer bruise in apex of right ventricle	Wound area in right ventricle Wound area in wall of left ventricle
Left ventricle. Pincer bruise in apex	Wound area in posterior wall of left ventricle. Bruised area in anterior surface of apex. Wound area in muscle
Left ventricle	Wound area in wall of left ventricle
Left ventricle	Wound area in wall of left ventricle
Right ventricle	Wound area in wall of right ventricle
Right ventricle	Wound area in wall of right ventricle
Right ventricle	Wound area in wall of right ventricle
Left ventricle	Wound area in wall of left ventricle
Left ventricle	Wound area in wall of left ventricle
Left ventricle	Wound area in wall of left ventricle
Left ventricle	Wound area in wall of left ventricle
Left and right ventricles	Wound area in wall of left ventricle
Left ventricle	Wound area in wall of left ventricle
Left ventricle	Wound area in wall of left ventricle
Left ventricle	Wound area in wall of left ventricle

(Cont.)

No. of Animal	Time of Killing	General Macroscopic Finding at Autopsy	Macroscopic Changes in the Heart
69	1st hour		No coagula in ventricles
70	10th hour		No coagula in ventricles
71	9th hour		Small coagulum in right ventricle. Minor infarct in lower lobe of left lung
72	8th hour		Small amount of coagula in both ventricles
74	7th hour		Small amount of coagula in both ventricles
76		20 hours postoperatively found dead	Small coagula in both ventricles
78	6th day		No coagula in auricles or ventricles
79	7th day		Pericardium adherent to anterior thoracic wall. Small coagula in right auricle
85	44th day	Operation repeated 44 days after first operation	Pericardium adherent to anterior wall of heart
86	9th day		Pericardium adherent to anterior thoracic wall
87	9th day		Pericardium adherent to anterior thoracic wall and wound area of heart. Small amount of clear fluid in pericardium
88	6th day		Pericardium partially adherent to heart wall
89	8th day		Pericardium adherent to anterior thoracic wall and wound area of heart
90		Died on 51st postoperative day in a fight	Pericardium adherent to anterior thoracic wall. Right heart enlargement
92	38th day		Pericardium adherent to anterior thoracic wall and wound area of heart. Enlargement of heart, especially to right
93		58 days after operation found dead (lacerated by rat).	Pericardium adherent to anterior thoracic wall and wound area of heart. Gelatinous material in right ventricle
94	35th day		Pericardium firmly adherent to wound area of heart
95		Died 3 days after operation	Heart greatly enlarged, especially on right. Coagula in auricles and ventricles. Fluid in both pleurae
96	35th day		Heart enlarged on right and left
100	25th day		Pericardium adherent to anterior thoracic wall and wound area of heart

Location of Penetrating Wound	Site of Histological Specimen
Left ventricle. Pincer bruise in apex	Wound area in wall of left ventricle Wound area in apex
Left ventricle	Wound area in wall of left ventricle
Left ventricle	Wound area in left ventricle
Left ventricle	Wound area in wall of left ventricle
Left ventricle	Wound area in wall of left ventricle
Left atrium. Pincer bruise in apex	Wound area in wall of left atrium
Right atrium	Wound area in wall of right atrium
Right atrium	Wound area in wall of right atrium
Auricle of left atrium. Pincer bruise	Wound area in auricle of left atrium. Pincer bruise in anterior surface of heart
Auricle of left atrium	Wound area in auricle of left atrium
Left ventricle	Wound area in wall of left ventricle
Right and left ventricles. Not sutured	Wound area in wall of left ventricle
Left ventricle. Surface of right ventricle. Wounds not sutured	Wound area in wall of left ventricle. Wound area in right ventricle
Through the entire heart	Wound areas in walls of left and right ventricles. Cicatrised area in septum
Through the entire heart	Wound area in walls of left and right ventricles. Scar area in septum
Through entire heart	Wound area in walls of left and right ventricles. Scar area in septum
Left ventricle	Wound area in wall of left ventricle
Through entire heart	Wound area in walls of left and right ventricles. Scar area in septum
Left and right ventricles	Wound area in walls of left and right ventricles
Left ventricle. Pincer bruise in apex	Wound area in wall of left ventricle

up by the apex with pincers or with help of the sutures. One of the heart cavities was perforated with an iridectomy knife, and after the onset of a gush of blood the wound was sutured with silk or catgut. The wound was then closed in layers. The experimental series is listed in table 1.

Following the operation the animals were killed by a blow on the neck, at first at intervals of 1 hour and later of 1 day. Samples of the traumatised parts of the heart were taken at autopsy for microscopic study. For comparison, samples were also taken from the cicatrising area of the pectoral muscles.

After the specimens were fixed in formalin and embedded in paraffin, sections were cut at 5 μ and stained by Weigert-v. Gieson, hematoxylin-eosin and resorcin-fuchsin elastic tissue staining methods.

RESULTS

Macroscopic Findings. — During the experiments, 13 rabbits were lost as a result of pneumothorax developing as a complication of the operation. In many cases the pneumothorax was bilateral. When unilateral, it usually did not produce untoward complications and at autopsy made a few days later it was found to have become resorbed. In addition to these 13 rabbits, 10 died during operation, several evidently of the ether narcosis and others possibly as a result of the manipulation of the heart. In 3 cases the cause of death was hemorrhage during operation and in 1 case infection of the pleural cavity which ran a stormy course following rupture of the pleura. Thus a total of 27 rabbits were lost due to complications.

At autopsy the pericardium was found to be adherent to the posterior surface of the sternum already one day after treatment. At this time the adhesions still consisted of fibrin. Such adhesions were seen at the autopsies of 40 rabbits.

In addition to being adherent to the anterior thoracic wall, the pericardium almost regularly had developed adhesions to the sutured area in the heart (29 cases). In 14 animals the adhesions were more extensive. No adhesions between the pericardium and the heart were observed as yet in samples taken less than 2 days after treatment. In no case was the entire pericardial cavity obliterated. Fluid was present in the pericardium of 10 animals from 2 to 35 days after operation.

Injury to the endocardium had produced coagula in both ventricles. On the left the coagula occurred earlier than on the right. In the left heart, coagula were seen in 8 cases from 7 hours to 7 days after operation. In the right heart there were coagula in 21 cases from 2 hours to 58 days after operation.

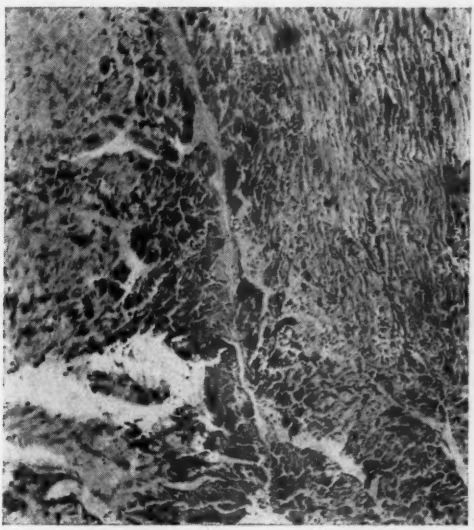

Fig. 1. — The wound is seen in the centre as a narrow slit containing fibrin in its cavity. Staining of the muscle at the edges of the wound is unusual. Profuse blood in the interstices. Sample taken 1 hour after production of the wound by incision.

Pulmonary infarcts apparently caused by the circulation of a coagulum was seen in 3 cases 9 hours to 69 days after operation. Seven rabbits died during the observation period between the 3rd and the 69th postoperative day. The cause of death in these cases could not be definitely determined but emboli undoubtedly played some part.

Cicatricial insufficiency in the form of a bulge was observed in 3 rabbits 39—48 days postoperatively. In addition, 3 rabbits showed a definite dilatation of the right ventricle 3—51 days after operation. In 99 rabbits dilatation of the heart occurred on both sides.

Microscopic Findings. — In the samples taken 1 hour after suture of the wound, the wound cavity was filled with fibrin (fig. 1).

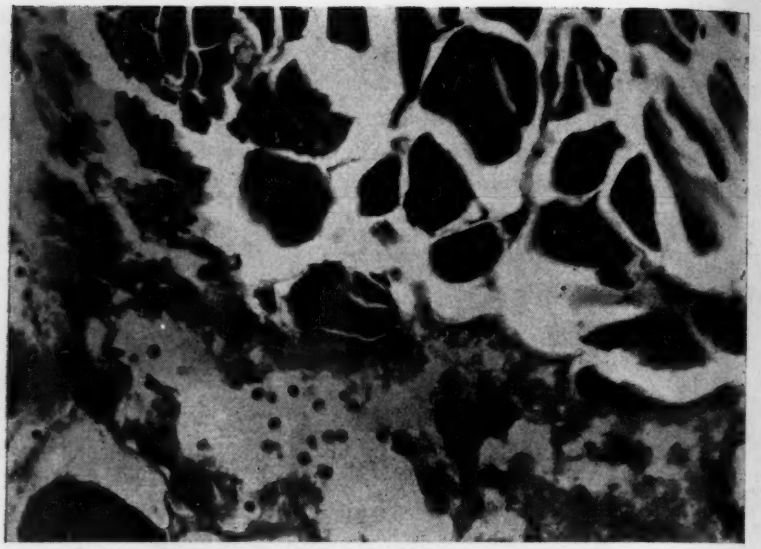

Fig. 2. — Muscle fibres seem hyalinised. So-called retraction caps are seen at the ends of the fibres. Incipient infiltration. Sample taken at 4 hours.

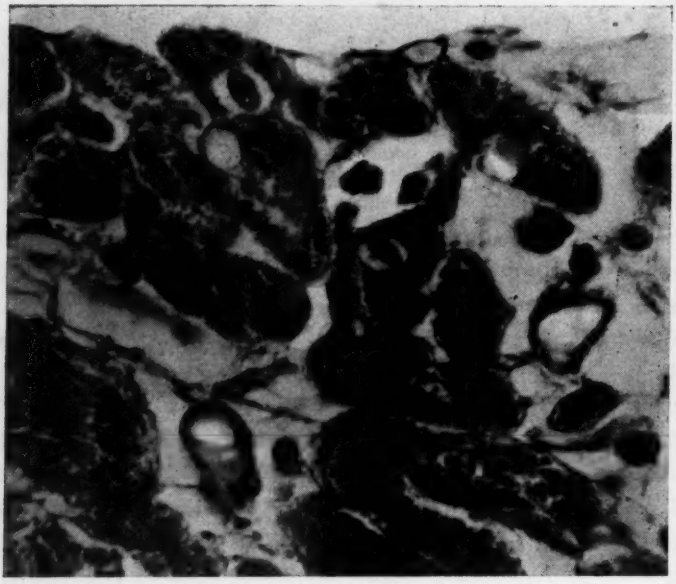

Fig. 3. — Muscle fibres at edges of the wound have lost their structure. Large nuclei in the capillary endothelium. Sample taken at 5 hours.

In the samples taken at 3 hours there was incipient infiltration at the edges of the wound, the cells increasing in number from the periphery towards the wound. The fibres in the muscular interstices were loose and the tissue was edematous. Four hours after

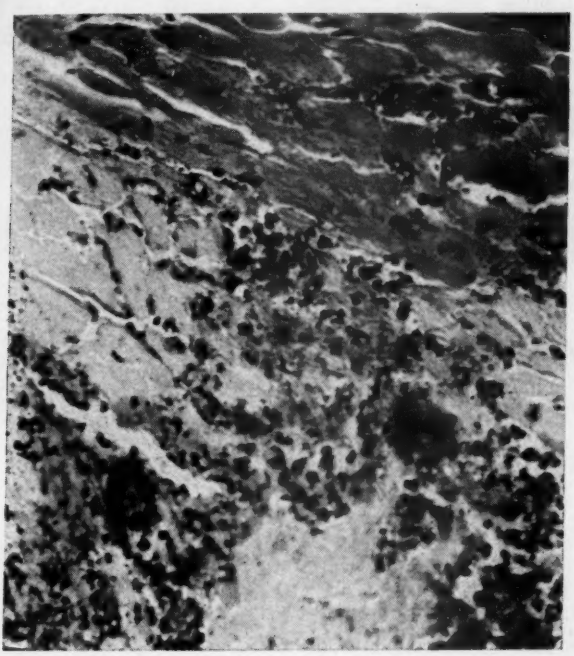

Fig. 4. — Infiltration is clearly seen, increasing towards the wound. Sample taken at 6 hours.

production of the lesion the muscle fibres at the edges of the wound appeared hyalinised and the muscle striae began to blur but did not completely disappear (fig. 2 and 3). The ends of longitudinal muscle fibres at the wound edges had a necrotic retraction cap. Already at this stage cellular infiltration was moderately great (fig. 4). It was most marked in the interstices between the muscle fibres and around the blood vessels. A constant, even increase of the cellular infiltration occurred during the first day and the number of cells in the tissue were increased both absolutely and relatively. The infiltrating cells were predominantly segmented cells and mononuclear cells. The latter varied morphologically over a wide range; their nuclei especially were variable in size

and shap. The cellular infiltration stopped at the margin of the necrotic area. There usually was a line of demarcation between the infiltrated and uninfiltrated areas. The capillary endothelial cells also were large and swollen in the 24-hour samples.

The process was not confined to muscle only, and accumulations of fibrin were seen also at the surface of the epicardium.

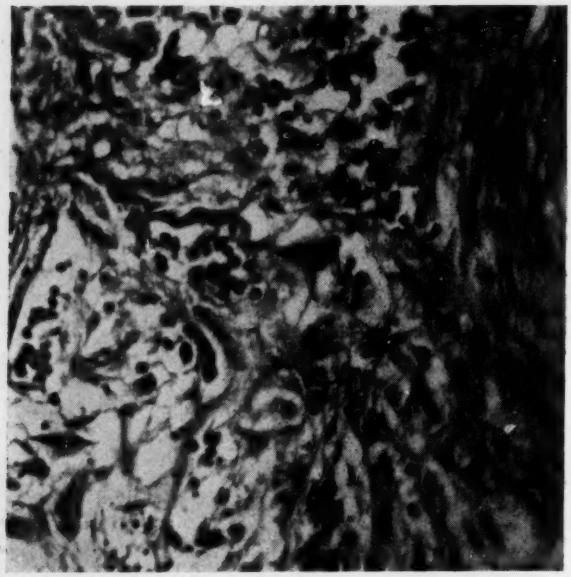

Fig. 5. — A large number of newly formed capillaries and perivascular infiltrations are visible. Cells are chiefly mononuclear. Sample taken on the 3rd day.

Furthermore the cellular infiltration was usually more marked in the vicinity of the epicardium than deeper within the muscle.

During the second day the edema in the tissues increased and the interstitial fibres were loose. In the sample taken at 48 hours the nuclei of fibrocytes, which usually were long and narrow, were swollen and their nuclei took a brilliant stain. The capillary endothelium was still edematous and the cells began to proliferate. In the vascular walls there were nucleated blood cells, most of which were mononuclear.

The cellular infiltration increased constantly during the second day and invaded in the direction of the centre of the wound. A considerable proportion of the infiltration cells were segmented

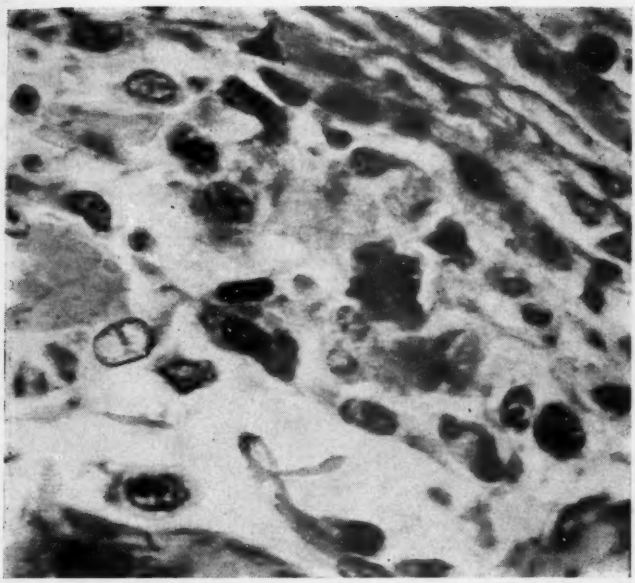

Fig. 6. — The varied morphology of the cellular infiltration can be clearly seen. Sample taken on the 3rd day.

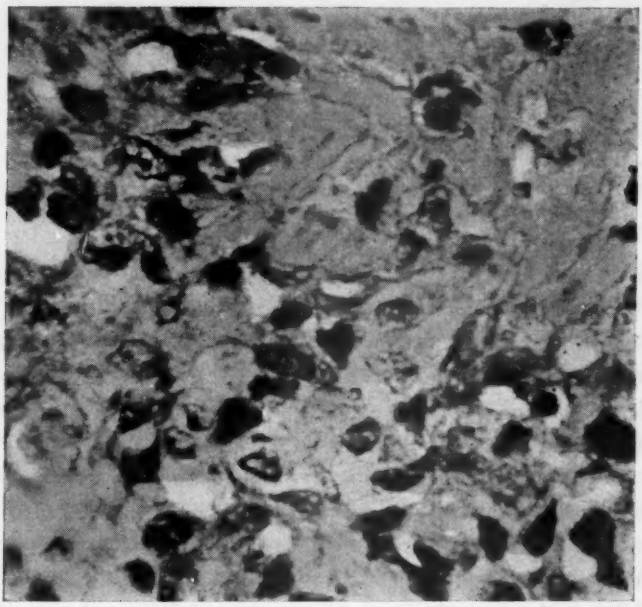

Fig. 7. — Infiltration is profuse at the edge of the wound. It is localised in the interstitial tissue. Muscular structure is indefinite. Sample taken on the 3rd day.

leukocytes, in which no phagocytic activity could be demonstrated. The samples taken at 48 hours showed degenerative changes, consisting in loss of sharpness of the cell margins.

On the third day after production of the lesion the marked edema continued and the infiltration increased constantly (figs. 5, 6 and 7). Proliferation began in the capillary endothelia. Protuberances pushed out from the protoplasm and united with

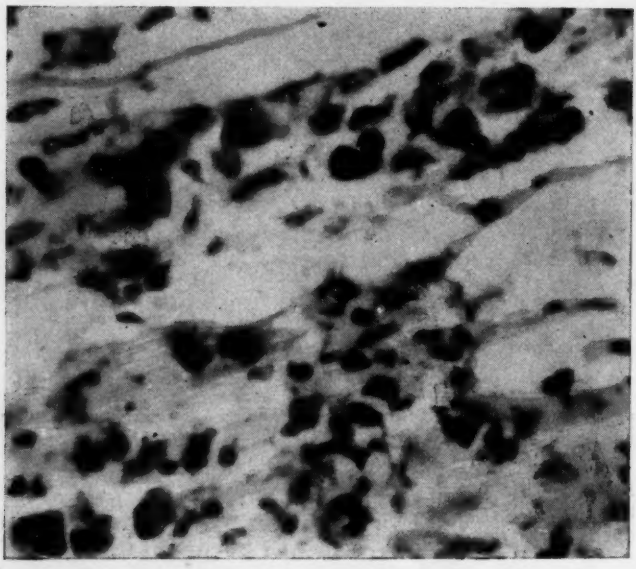

Fig. 8. — Newly formed capillaries and the accompanying cellular infiltration. Macrophages are also visible. Sample taken on the 4th day.

protuberances sent out by other capillaries. They formed a network whose lumen communicated with the lumina of the original capillaries. The process at this stage occurred in the periphery of the wound area, whence it proceeded towards the centre. The samples taken on the third day also showed fibrocytes undergoing division in the muscle interstices at the edges of the wound. At the edges there was infiltration of macrophages and the first signs were seen of necrotic tissue being carried away. This process also began at the periphery, proceeding towards the centre. The macrophages caused fragmentation of the necrotic end of muscle fibres. They generally were pigmented, the pigment consisting of hemosiderin and lipofuscin.

During the third day the process had a similar course in all parts of the wound, even if the infiltration was most marked on the epicardial surface.

On the fourth day the cellular infiltration progressed (fig. 8). The cells formed dense groups, making their differentiation difficult. Degeneration of segmented leukocytes was abundant; a part of these cells were in a state of complete decomposition. Eosinophile leukocytes, although present in small numbers, were a new feature.

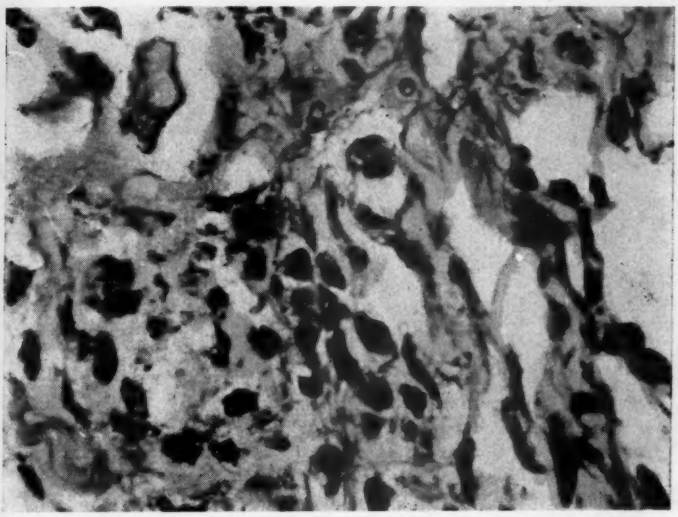

Fig. 9. — Collagenous fibres are present. The perivascular infiltration is still moderately abundant. Sample taken on the 9th day.

The regenerated capillaries proceeding towards the centre of the wound contained red cells. The cells in the loose interstitial connective tissue in the vascular walls were undergoing mitosis, and mitotic figures were also seen in the loose connective tissue.

During the fifth, sixth and seventh days the process progressed actively. A change, however, was taking place in its character. The infiltration by segmented cells gradually decreased and the cells showed marked degenerative changes. Well preserved eosinophils were nevertheless present. The number of capillaries was large. Young undifferentiated basophilic fibroblasts were seen in large numbers and they accompanied the newly formed capillaries into the area of the wound. The samples taken on the seventh day

also showed the first perivascularly situated collagenous fibres. The number of macrophages was moderately abundant.

On the eighth day the segmented leukocytes continued to decrease and they showed abundant degenerative changes. The number of macrophages was still moderate. Phagocytosis was seen in their plasma. There was an abundance of mitotic figures in the tissue. Cords of cells had also appeared, running parallel with the capillaries. Capillaries were still present in large numbers. Incipient collagen formation was evident (fig. 9).

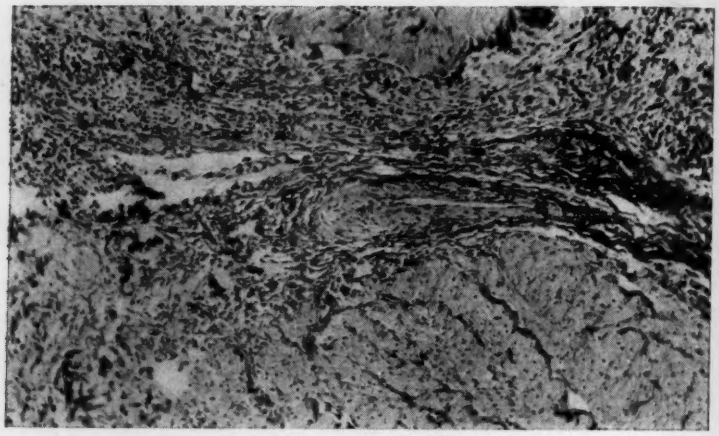

Fig. 10. — Scar tissue rich in cells and capillaries fills the wound cavity. Necrotic fibres still visible in the centre. Sample taken on the 16th day.

During the second week the segmented cell infiltration continued to decrease gradually. In the centre of the wound most specimens still showed a small amount of necrotic tissue. There was an abundance of pigmented macrophages.

Fourteen days after production of the lesion the segmented cells were present only in very small numbers in a few places. Usually the necrotic tissue had disappeared, with the exception of small islands in the centre of the wound cavity. Macrophage activity also decreased. The wound cavity was filled with granulation tissue rich in cells and capillaries (fig. 10). Collagenous fibres were abundant.

Three weeks after production of the lesion the segmented cell infiltration was practically absent and the number of macrophages

had decreased abruptly. A delicate connective tissue joined the interstices on the two sides of the wound. The connective tissue was moderately rich in cells, although the cell content clearly decreased during this week. Collagen was present in larger amounts and the capillaries disappeared.

Four weeks after production of the lesion the leukocytes had entirely disappeared from the samples and only a few macrophages

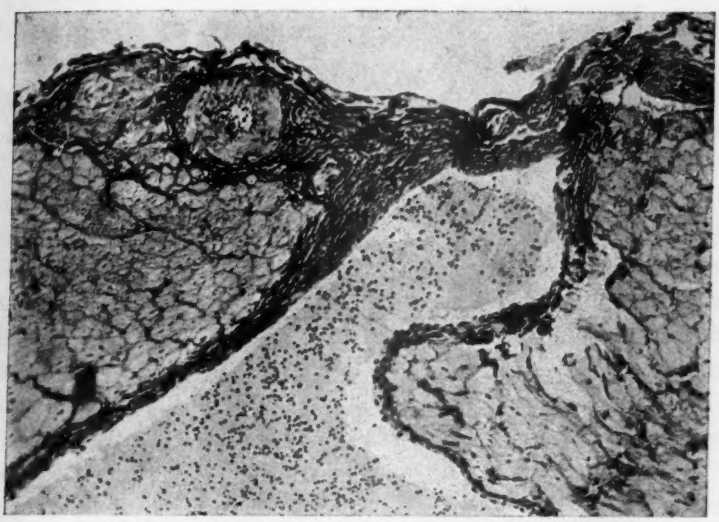

Fig. 11. — Coarse-fibred scar of collagenous connective tissue in the wall of right auricle. Very few cells are present in the scar tissue. Sample taken on the 165th day.

were seen. The number of capillaries in the scar area was also small. The cell content of the connective tissue also decreased gradually and the amount of collagen increased.

During the second month the number of cells in the scar tissue progressively decreased and considerable shrinkage of the scar was evident. Some isolated macrophages were still present. With continued decrease of the cell content the amount of collagen increased.

In the samples taken three months after the lesion the scar tissue was poor in cells and was composed of collagen. In samples taken one year after the lesion there was a contracted, collagenous scar which separated the ends of muscle fibres but at the same time had restored their continuity (fig. 11).

During the experiment no signs were seen in the heart muscle pointing to the regeneration of muscle. During healing there always formed a connective tissue scar which underwent shrinkage during the lengthy observation period and one year after the lesion formed only a thin sheet between the ends of the muscle fibres.

The samples revealed definite retardation of healing in those cases in which a hematoma developed in the wound cavity (fig. 12), or

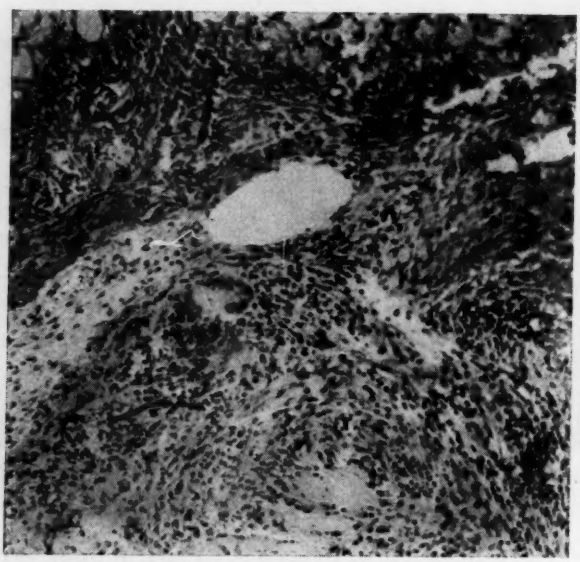

Fig. 12. — In the centre of the picture a hematoma cavity, surrounded by scar tissue rich in cells.

in which the suture material was too near the wound cavity, giving rise to constant irritation. In these cases abundant segmented cell infiltration continued for four and five weeks after production of the lesion. Fibroplasia also was delayed in these cases. In some cases a cavity was formed in the centre of the hematoma and its filling retarded the development of a uniform scar. In samples taken at two months this formation was still clearly visible in the centre of the scar, where otherwise very few cells remained. The end result also in these cases seemed to be a uniform collagenous scar.

DISCUSSION

Mediastinotomy was performed on 100 rabbits under ether narcosis and a penetrating wound was made in the heart muscle. The wound was sutured with silk or catgut. The animals were killed by a blow on the neck various lengths of time after the operation, ranging from 1 hour to 1 year. The autopsy findings were noted and samples were taken for histological examination from the wound area in the heart. A comparatively large number of animals were lost, as rupture of the pleura could not always be avoided. Death due to anesthesia was considered to be the reason for the loss of 10 animals during the operation. Only 3 animals died of hemorrhage at operation, and infection was the cause of death of 1 animal.

Seven rabbits died spontaneously on the 3rd to 69th day of the observation period. Obviously this figure would have been higher had not a part of the animals been killed already from the first postoperative hour onwards. The probable cause of death was embolism, but no systematic histological examination for possible emboli was made. Three animals which were killed showed changes pointing to pulmonary embolism. In any case it seems apparent that embolism associated with a heart trauma is important as a cause of complications (cf. Boyd). This opinion is supported, for instance, by the finding of coagula in the ventricle in 30 animals. In two-thirds of the cases the coagula were situated in the right heart; this may probably be attributed to the slower flow of blood to the right, which is more conducive to the formation of coagula in an endocardial lesion than the blood stream in the left heart. The same circumstance may explain the finding of coagula in the left heart during a shorter period of time than in the right heart (left heart, 7 hours to 7 days; right heart, 2 hours to 58 days). Coagula might have been present in a larger number of hearts, but owing to the sacrificing of the animals at various period after operation, coagula either had not yet formed or had already disappeared. However, the coagula apparently did not have a marked tendency to circulate, since the number of complicated cases was relatively low in relation to this high incidence of coagula. It seems probable that they gradually dissolved by enzymic action. (Cf. Haecker and Anderson).

The histological examination revealed no signs of organisation of endocardial thrombi.

Macroscopically the progress of the wound healing process was followed by observing the accumulation of fluid, development of adhesions and distention of scars. There were no cases of rupture of the heart. (Cf. Edmonson and Hoxie, and Waern.) In a total of 10 animals the pericardial fluid was increased. This observation was made 2 to 35 days postoperatively. The accumulation of fluid probably was practically a regular occurrence as a result of the inflammatory component of the healing process. The incised tissue areas also developed adhesions. Already 1 day postoperatively there were adhesions of fibrin between the pericardium and the posterior surface of the sternum. Probably due to the heart movements, adhesions were not present between the layers of the pericardium before the second postoperative day. The pericardium was adherent to the wound area in the heart in nearly every case. Frequently there also were adhesions over a larger area (Boyd). In not a single case was the entire pericardial cavity obliterated (cf. Bright and Beck). The development of adhesions may have been prevented in part by the accumulation of fluid. Insufficient scar formation was seen only in 3 rabbits during the 39th to 48th day. The incidence of this condition would probably have been higher if all the animals had been allowed to live longer and if the wounds had been larger in size. (Cf. Anderson, Elsberg, and Bailey.)

It was seen in the microscopic examinations that the exudative phase in the wound began already 1 hour after the operation. The wound cavity was filled with masses of fibrin. In the edges of the wound, the area bordering upon the incision showed signs of necrosis involving chiefly the muscle fibres. The blood vessels and connective tissue did not become necrotic to the same degree. The capillaries were filled with blood and petechial hemorrhages were seen also in the tissue. (Cf. Mallory *et al.*) At this time the first signs of cellular infiltration were also seen. As in incision wounds of the skin, the cellular infiltration began in the periphery of the wound area, from which it progressed by stages towards the centre (Allgöwer). Infiltration was observed in the edges of the wound already during the first hours after the operation, whereas Mallory *et al.* reported that in the marginal area of infarcts it is present only after 24 hours. However, an exception was seen in the cases in which, for some reason, for example tightness due to suturation, a more extensive necrotic area developed in the wound area.

The healing of such a wound resembled the histological observations of Mallory, White and Salcedo-Salgar on the healing of myocardial infarcts during the first few days. It is important for the healing of the wound that the suturing material is as little irritating as possible and the suture made as exact as possible in order to avoid the formation of hematomas which retard the healing; however, the sutures must not be unnecessarily tight or placed at too short intervals. In two cases of this kind there was, 4—5 weeks after operation, abundant inflammatory infiltration in the wound and fibroplasia was greatly delayed. Furthermore in one test animal a hematoma cavity had formed in the centre of the scar tissue in the myocardium. These developments have the effect of retarding scar formation and weakening the wound area. Cellular infiltration in the heart muscle begins at the same time as in incision wounds and it is more marked on the epicardial surface than in muscle.

The second component in wound healing, fibroplasia, began in the hearts 48 hours after the operation; at this time changes were seen in the nuclei of fibrocytes and in the capillary endothelium (Sandblom 1944). Already during the third day new capillaries began to form and fibrocytes divide in the periphery of the wound. On the 5th, 6th and 7th days this process was active but of an altered nature, as the segmented cells gradually decreased in number. According to Mallory *et al.*, leukocytes do not phagocytise but, on being decomposed, form an enzyme which disintegrates the necrotic muscle and assists in its phagocytosis. The macrophages perform the latter action, a proof of which is considered to be the pigment found in the macrophages. During the 7th day the first collagenous fibres were seen. Their formation was chiefly centred around the blood vessels. At this time the specimens contained a very large number of macrophages, which were carrying away necrotic material.

Two weeks postoperatively the number of macrophages had greatly declined and the necrotic material had been disposed off almost completely. The number of segmented cells was also quite small and the wound cavity was filled with granulation tissue rich in cells and capillaries. Collagenous fibres were abundant at this stage. In a normal wound the cellular infiltration disappears almost entirely within 4—5 weeks and there follows increased formation of collagen and contraction of the scar. The collagenous scar in heart

muscle is seen at a later stage than in the usual incision wounds, possibly because of the continued contractions of the heart muscle. The end result was a uniform scar poor in cells, which joined the edges of the muscle.

There was an unexpectedly great similarity in the healing process of the heart wound and that of infarction as described by Mallory *et al.* Also in point of time the inflammatory reaction and fibroplasia in these experimentally produced heart wounds and in infarcts examined at autopsy occurred at nearly the same time, although the course of events in the healthy rabbit heart was more rapid.

In the pericardium the events were found to accompany those in the muscle wound, and the pericardial scar was adherent to the myocardial scar. (Cf. Crynes and Hunter, and Warburg.)

Fischer suggested, among others, that regeneration of muscle fibres takes place in wounds in the heart muscle, but we were unable to find any signs pointing to such regeneration, whereas a »retraction cap» enclosed in perimycium was formed at the end of the fibres (cf. Howes). The scar tissue was connected to the interstices of muscle fibres, and contraction of the scar pulled the ends of the fibres close to each other (cf. Elsberg).

The histological analysis of the heart wound indicated certain points to which attention should be paid at operation in order to promote favorable scar formation. The suturing material must be of a kind that does not irritate the tissues. Care should be taken that the sutures are not unnecessarily tight, as this also causes necrosis, and the development of a hematoma in the wound affects unfavorably the prognosis of healing.

With a view to postoperative treatment, the observations made in the present investigation brought out certain points of importance. Thus the possibilities offered by anticoagulants should be taken into consideration in the prophylaxis and treatment of coagula formed in the ventricles. Intracardiac coagula develop chiefly during the first postoperative week, when edema in the traumatised tissue is heaviest. Fluid accumulation in the pericardium may produce other complications as a result of impaired heart function. Copious collection of exudate may also directly produce cardiac tamponade.

It was observed in the histological examination that owing to cellular infiltration and necrosis the strength of the tissue is poorest

during the second week. It begins to improve during the third week as a result of the formation of collagen. With a view to ruptures and stretching of the scar it is important that the heart muscle is not subjected unduly to strain, for according to Edmonson and Hoxie cardiac rupture is three times as common if the blood pressure after, for instance, infarction is 140 mm/Hg or higher than when the pressure is normal or subnormal. Waern, among others, recommended that heart patients should be confined to bed for 4—6 weeks to give the scar time to increase in strength.

After the healing of a heart trauma it is not usually possible to evaluate the damage caused to heart function by the lesion. Adhesions in the pericardium possibly have no significant effect on the function. A well healed scar in the heart muscle possibly forms no hindrance to satisfactory function. Probably the deleterious effect of a scar is greatest when the cicatrised area has become distended, i.e., when an aneurysm has developed.

SUMMARY

In 100 healthy adult rabbits a wound penetrating the wall of the heart was made with an iridectomy knife under ether anesthesia. After onset of a blood gush the wound was sutured with silk or catgut. The animals were killed at various intervals by a blow on the neck and specimens of the wound area were taken for microscopic examination.

A very common macroscopic finding was adherence of the pericardium to the wound area in the heart (29 cases); more extensive adherences were present in 14 cases. Coagula resulting from the endocardial trauma were seen in the right heart in 21 cases and in the left heart in only 9 cases. Insufficient scar formation manifesting as bulging of the scar was present in 3 rabbits.

The microscopic examination showed that the healing of a heart wound accompanies chronologically and cytologically the healing of the wound produced in striated muscle. As a result of the healing process a collagenous scar is formed, joining the muscular edges of the wound. Definite signs pointing to regeneration of the heart muscle were not seen in these experiments. Retarded healing of the wound was observed in cases in which a hematoma had developed in the wound cavity or in which the suture material was placed too close to the wound cavity, causing continuous irritation.

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